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Article Review

Multiple Sclerosis: Current Knowledge of the Pathology and Use of Monoclonal Antibodies as a Promising Therapy

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Abstract

Multiple sclerosis is an autoimmune condition characterized by an inflammatory condition and neuron demyelination, leading to a significant deterioration in the patient's quality of life as the disease progresses. The immune system reactivity in this pathology is mainly mediated by reactive T lymphocytes against myelin. The harmful substances production and proinflammatory cell infiltration occur. Currently, there is no cure, so treatment focuses on reducing the development of the individual's long-term disability by addressing symptoms, acute exacerbations, and slowing progress. The traditional treatment includes immunosuppressive substances such as corticosteroids and interferons. However, an approach to more specific, highly effective therapies such as monoclonal antibodies is currently being sought. Ofatumumab, ocrelizumab, alemtuzumab, and rituximab are commercialized monoclonal antibodies. Likewise, therapies in the research phase, such as ublituximab, inebilizumab, GNbAC1, and elezanumab, can be found. Therefore, research must continue to have more information to increase the availability of therapeutic options for patients.

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INTRODUCTION

The immune system is the body's tissues, organs, and cells that help fight infections and diseases. It is characterized by having an extensive antigen repertoire for pathogen detection, generating an immune memory, repeating a response quickly after a first infection, and tolerating tissues recognized as own. An antigen is any molecule that causes activation of its effector cells. An autoimmune condition can progress when a body molecule activates them, and the immune response is generated. These pathologies produce antibodies to self-antigens, provoking tissue and cell damage[1].

Multiple sclerosis (MS) has one of the highest prevalences in the population. By 2015, it was number 10 in prevalence among neurological problems worldwide, with more than two million cases[2]. It affects the central nervous system (CNS), causing neuron demyelination and damage to other nervous tissues. Subsequently, scarring occurs, with the consequent involvement of axon connections and even neuronal death[3]. Clinically, it manifests as a loss of patient physiological functions, classified into primary symptoms (visual problems, paresthesia, pain, weakness, ataxia, slurred speech, fatigue, tremor, and sexual dysfunction), secondary (urinary calculi, osteomyelitis, osteoporosis, respiratory infections, poor nutrition, and depression), and tertiary (financial, personal, social, and emotional problems)[4]. This condition has no cure, and its treatment is based on symptomatic management. It has different stages in its progression, each with its pharmacological management. Initially, it is based on glucocorticoids, suppressing the secretion of inflammatory mediators, such as cytokines, by T lymphocytes and eliminating the inflammatory T cells through apoptosis[5].

In more advanced phases, options based on the individual's immunosuppression can modify the disorder course. Some examples are interferon β (INF-β) and glatiramer acetate[6]. Other drugs are monoclonal antibodies. These are molecules

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made in a laboratory that act on specific cell targets, similar to the effector elements of the immune system[7]. Historically, they have been considered as a second-line option. It can be indicated as the first line if no option is available[8]. They are not utilized in the first instance due to the possibility of severe adverse effects. Another reason is the possibility of generating an immune response against the molecule, rendering the therapy ineffective with each administered dose[9,10]. Technological advances have allowed monoclonal antibody development with more significant clinical efficacy. Therefore, this review aims to synthesize its use as a therapeutic opportunity against MS based on existing knowledge about this illness.

MULTIPLE SCLEROSIS PHYSIOPHATOLOGY

The CNS comprises the brain and spinal cord, structures covered by three connective tissue membranes called meninges[11,12]. Cells of the CNS differentiate into neurons and glial cells. They are functional components of the brain, known as the parenchyma. Neurons are divided into the soma or body (where the nucleus is found), the dendrites, the axon, and the presynaptic terminals. Maintenance functions such as protein synthesis are generally done in the soma. The dendrites are ramifications of the soma, and their primary function is the reception of information. At the same time, the axon is the central projection of the cell body, responsible for sending signals. Some axons have myelin, an electrical insulation. If it is myelinated, action potentials jump between the nodes of Ranvier, which lack this substance, between two adjacent sheaths. Otherwise, they travel continuously along such a projection[11].

On the other hand, glial cells are the most abundant and are constituted of microglia, astrocytes, and oligodendrocytes. Microglia are the first line of defense against antigens. As a complement, astrocytes are subdivided into fibrous and protoplasmic and have many functions, including neuron support, extracellular fluid regulation, supply of energy substrates such as glucose, and elements of the blood-brain barrier, formed around capillaries in the nervous system. Finally, oligodendrocytes are responsible for axon myelination[11-14].

Regarding MS, its manifestations involve inflammation, demyelination, and fibrous proliferation of glial cells or gliosis, with a greater tendency for optic nerves, periventricular white matter (located adjacent to the brain ventricles) of the brainstem, cerebellum, and spinal cord. Furthermore, neurons die from axonal loss[3,15-18]. Because of inflammation, plaques are generated around veins and venules, as detailed in **Figure 1**. At the microscopic level, there is perivenular cuffing by inflammatory mononuclear cells. They are embraced by a mononuclear infiltrate of cells located around the vessels, specifically macrophages and T lymphocytes, with myelin degradation products inside and infiltrating surrounding white matter. The infiltrates' composition may vary depending on the stage[3,15,19,20].

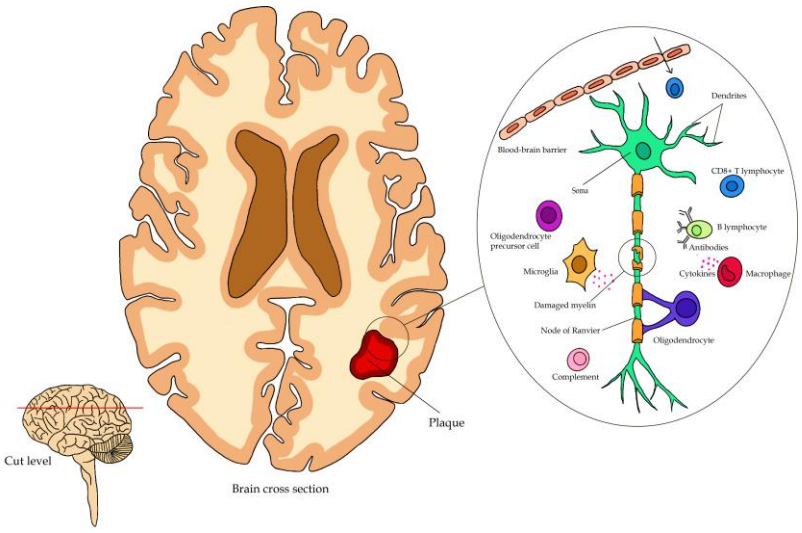

Figure 1. Cross section of the brain with plaques and the cellular content of the infiltrates around the blood vessels. The formation of plaques in the brain is shown macroscopically. At the microscopic level, these structures have cell infiltrates that transgress the blood-brain barrier, such as macrophages, T lymphocytes, and B cells, which produce antibodies against myelin. Activated complement cells and microglia, responsible for demyelination, are also found, and it is usual to locate oligodendrocyte precursor cells that survive the microglia actions.

Monocytes and macrophages stimulate the migration of T lymphocytes, transgressing the blood-brain barrier with subsequent entry into the CNS. Oligodendrocyte damage and demyelination arise due to the cytotoxic activities of microglia, antigen-presenting cells (APCs) in this area, and the release of harmful substances such as nitric oxide and other radicals[15,21]. B cells of the immune system also infiltrate the nervous system and produce anti-myelin antibodies. Therefore, these proteins are found in demyelinated sheaths and activated complements. In the plaques formed in MS, oligodendrocyte precursor cells survive, but they do not differentiate into mature cells, losing their ability to produce myelin[3,22].

Multiple sclerosis is divided into four types: relapsing-remitting (RRMS), primary progressive (PPMS), secondary progressive (SPMS), and clinically isolated syndrome (CIS)[3,8]. Its characteristics are established in **Table I**. Additionally, the inflammatory response of the remitting stage is linked to the focal infiltration of monocytes and lymphocytes into the perivenular parenchyma. In contrast, in progressive disease, it is attributed to disseminated microglial activation[3].

Table I. Types of MS and the main characteristics of each one.

Type	Characteristics
RRMS[3,15,23]	-Occurs in 85% of cases. -Continuous, discrete attacks, with the evolution of days or weeks, followed by periods of remission or partial or total recovery. - Appreciable symptoms between 24 and 48 hours. -Progressive attacks over time present less evident recovery. -A 50 to 60% of cases evolve to SPMS.
PPMS[3]	-Arises in 10% of cases. -Individuals do not experience attacks but continuous functional deterioration.
SPMS[3,22,23]	-Starts as RRMS. -Permanent damage to the myelin sheaths. -Continuous deterioration of neurological functions unrelated to the acute attacks. -Provokes much neurological disability.
CIS[24,25]	-A single episode of neural symptoms due to inflammatory demyelination. -Fever, encephalopathies, or infections do not accompany it. -It can be diagnosed as MS when a second attack develops. -In 85% of patients, RRMS can begin as CIS.

Another feature is the aggregates of T and B cells located in the meninges, the spaces surrounding arterioles, the fluid-filled capillaries and venules in the brain, known as perivascular spaces, and the brain parenchyma. It is attributed to progressive states[3,26]. Symptoms vary depending on the course and injury location in the CNS, with pain being common. Signs of neurological dysfunction, impaired vision, paresthesia, or (abnormal sensations in the stimulus absence, such as tingling), hypoesthesia (partial sensation loss), facial and limb weakness, spasticity (velocity-dependent increase in the muscle stretch reflex), ataxia (disorders of balance and coordination), and even vertigo are identified. Symptoms such as intestinal and urinary incontinence, sensitivity to heat, and sexual and cognitive dysfunction, among others, may occur[3,27-29].

MULTIPLE SCLEROSIS RELATED IMMUNOLOGY

The illness immunology is mediated by T lymphocytes reactive to myelin antigens. These cells are found in the peripheral blood of the individuals. Nevertheless, MS patients have more avidity and potency to induce inflammation[30]. Depending on the cytokines released, helper T lymphocytes (CD4+) are divided into Th1, Th2, and Th17. The same occurs in cytotoxic T cells (CD8+), whose subpopulations include Tc1, Tc2, and Tc17. Those expressed in the highest amount in MS are Th1, Th17, and Tc17. They secrete cytokines such as interleukin-17 (IL-17), granulocyte colony-stimulating factor (G-CSF), and IFN-γ[31,32]. IL-17 stimulates IL-6 and GM-CSF production. The latter is a granulopoiesis primary regulator, and the neutrophils are released in the bone marrow[33]. For its part, IFN-γ improves the antigens recognition by CD4+ T lymphocytes, augments reactive oxygen species (ROS) production, and contributes to the activity of CD4+ and CD8+ T cells and the antibody generation[34].

The T cell activity is closely related to the B lymphocyte interaction. In MS, B cells have an abnormal cytochemical profile, inducing aberrant pro-inflammatory T cell responses due to the production of an amplified amount of pro-inflammatory cytokines such as IL-6, GM-CSF, and tumor necrosis factor-α (TNF-α). At the same time, there is a deficiency in regulatory

molecule production, such as IL-35 and transforming growth factor-β (TFG-β)31. A summary of the various functions of these substances is shown in **Table II**.

As a complement, mononuclear cell infiltration is frequent in acute lesions, especially macrophages and T cells. However, 25% of this count corresponds to B lymphocytes[35]. The infiltrate amount is more significant than other inflammatory SNC conditions, especially in early stages and active lesions[31]. In turn, it is known that the number of CD8+ T cells is higher than that of CD4+ T lymphocytes, regardless of the MS subtype and its progression[35].

Table II. Functions of cytokines involved in MS.

Cytokine	Functions
IL-17[33]	It induces IL-6 and G-CSF synthesis.
G-CSF y GM-CSF[33]	Granulopoiesis regulator and participates in neutrophils release. GM-CSF is specific for macrophages.
IL-6[36]	Recruitment of neutrophils and monocytes.
IFN-γ[34]	It improves antigenic recognition by APCs, maintains the activity of CD4+ and CD8+ T lymphocytes, rises ROS release, and contributes to antibody production.
TNF-α[37]	It has two signaling pathways. The TNF1 receptor is associated with cytotoxic responses because of programmed cell death and proinflammatory responses. The TNF2 receptor is involved in cell activation, migration and proliferation, and tissue regeneration.
IL-35[38]	Immunosuppressive activity, by promoting regulatory T and B cells, while suppressing effector T cells and macrophages.
TFG-β[39]	Potent inhibitor of T lymphocyte proliferation and promoter of cell death in activated T cells.

EPIDEMIOLOGY

Multiple sclerosis affects approximately 2.5 million people worldwide[3]. The number of women is two or three times higher than that of men. Likewise, it can occur at any age since 10% of cases occur in children under 18[40]. In recent years, prevalence has increased globally[41]. Some regions show a higher value, such as Scotland. For 2020, 376 events per 100,000 inhabitants were estimated for people 15 or older[42]. Another region with higher data is Northern Ireland, given that 238.4 cases per 100,000 inhabitants were projected for 2018[43].

For its part, in African and East Asian countries, it is low[15]. Recent data from the United Arab Emirates and Kuwait showed rates of 55 to 85 events per 100,000 population[44]. In the Americas, in 2017, roughly 850,000 to 915,000 people over 17 years of age lived with MS in the United States (around 338 to 363 cases per 100,000 inhabitants)[45]. Canada is another country with an appreciable number of patients. The value is around 93,500 individuals[46].

At the Latin American level, a study published in 2013 mentioned that the nations with the lowest prevalence were Panama, Ecuador, and Colombia, while Brazil and Argentina had high rates of up to 21.5 cases per 100,000 inhabitants[47]. Generally, the territories with the highest European migration and regions further away from the terrestrial equator tend to have more events[48]. Finally, in Costa Rica, a prevalence of 8.9 cases per 100,000 inhabitants was obtained and an incidence of 8.3 per million inhabitants in 2017, with a predominance of females. In addition, the percentages are detailed according to the variant type: 2.7% PPMS and 16.2% SPMS[49].

DIAGNOSIS

One MS characteristic is the lack of specific markers for its diagnosis. For its identification, the medical history and neurological examination are considered[50]. For this reason, it is elaborated by eliminating other possible causes or pathologies4. Within the diagnostic criteria, the individual must have two or more symptomatic episodes (for example, frequent pain, dizziness, and cognitive dysfunction) and two or more signs (including optic neuritis, partial spinal cord syndromes, and intranuclear ophthalmoplegia) reflecting an alteration of the CNS white matter. Moreover, the attacks must occur for more than 24 hours and be repeated in periods more remarkable than a month[3,51,52].

As primary studies evaluate its presence or absence, there are several methods. They embrace cranial, cervical, and thoracic magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) analysis, and blood tests[50]. Of the previous tests, the consolidated tool is MRI. It is a noninvasive technology that generates detailed images of almost every internal structure in the human body, including the organs, bones, muscles, and blood vessels. The scanners create images through a large magnet and radio waves[53].

This procedure requires contrast substances to improve and facilitate the diagnosis, specifically intravenous gadolinium[50]. This substance, classified as ferromagnetic (aligns with an external magnetic field), shortens the protons' relaxation time, increasing the signal and improving image quality[54]. Its application distinguishes whether the lesions are demyelinating or inflammatory, defining a differential diagnosis[50].

Another tool is CSF examination by lumbar puncture. This method reviews biochemical aspects such as glucose, protein, albumin, immunoglobulin G (IgG), lactate levels, and quantitative and qualitative tests for intrathecal IgG synthesis (oligoclonal band analysis)[4,50]. The data provide information on biomarkers involved in neurodegenerative diseases[55]. To establish a diagnosis through this process, it is expected to observe anomalies such as:

1. Lymphocytic mild pleocytosis[4].
2. Higher concentration of intrathecally synthesized IgG (produced within the CNS)[56,57] is characteristic of neurological infection and inflammatory disorders. Antibody production occurs typically in professional lymphoid organs such as the spleen, lymph nodes, and bone marrow. However, MS can occur within the CNS due to the ectopic germinal centers[57].
3. CSF total protein is usually normal or slightly elevated[4].
4. Two or more oligoclonal bands (occur in more than 85% of patients) represent the diagnostic biomarker since they indicate intrathecal synthesis of IgG[57].

In addition to the above, microbiological tests can be performed, such as cell count and enzyme-linked immunosorbent assay (ELISA), histopathological evaluation, and blood tests comprising complete blood count, kidney and liver function, electrolyte levels, sedimentation rate, vitamin D, thyroid function, and lipid panel. Furthermore, viral serology exams are carried out against human immunodeficiency virus (anti-HIV), hepatitis C (anti-HCV), and antinuclear antibodies (ANA), among others[50]. ELISA is the gold standard of immunoassays. It is susceptible and is contemplated for detecting and quantifying substances, such as antibodies, antigens, proteins, glycoproteins, and hormones. The detection is accomplished by complexing antibodies and antigens to generate a measurable result[58].

As secondary detection techniques, there are evoked potentials through electrical potentials triggered by repetitive stimulation like exposure to light, sound, and touch. It seeks to measure electrical activity in brain areas to demonstrate the demyelination impact[59]. Likewise, optical coherence tomography[50] and urodynamic tests such as flowmetry, cystomanometry, and urethral pressure profile[60,61] are available. Cognitive tests, summarized in a cluster called the Brief Repeatable Battery of Neuropsychological Test (BRB-N), are also accessible. They include tests to determine attention, memory, concentration, and learning[62,63]. Finally, tests for infectious etiologies, angiography, examination of the eye, hearing tests, electrophysiological studies, and cardiac examination are done for a differential diagnosis. All this information rules out other conditions with similar symptoms[50]. Some are described in **Table III**.

Table III. Differential diagnosis of MS.

Pathology	Characteristics
Neurosarcoidosis[64]	Multisystem inflammatory pathology characterized by noncaseating granulomas with neurologic organ system manifestations.
Vasculitis[65]	Autoimmune disease secondary to inflammation induced by cytokines, causing a blood-brain barrier dysfunction.
CNS lymphoma[66]	Rare brain tumor that develops neurological symptoms easily overlapped with MS.
Lyme disease[67]	Infectious illness whose pathogen is *Borrelia burgdorferi*, transmitted by ticks, provoking neuropathy symptoms such as paresthesia, ataxia, and demyelination. It should be considered for its endemic areas.

TRADITIONAL TREATMENTS

Since there is no cure for MS, its treatment seeks to improve the patient's quality of life and reduce the development of long-term disability. Thus, the therapeutic approach has three aspects: symptomatology, recovery from acute exacerbations, and slowing down their progress[4], detailed below.

Symptomatology

Non-pharmacological support is sought to address the symptomatic picture as a first option. Cognitive behavior therapy is recommended for managing cognitive and psychiatric symptoms, physical therapy for gait problems and ataxia,

temperature control for thermosensitivity, and rehabilitation and aerobics for fatigue and sleep. Some studies mention using modafinil, a neurostimulant drug, to relieve fatigue and hypersleepiness. Besides, amantadine is accessible. Regarding pain relief, the anticonvulsants gabapentin, pregabalin, lamotrigine and topiramate have been considered[68]. As an adjunct, anticholinergic and antimuscarinic agents are available for urodynamic illnesses, while sexual dysfunction can be addressed with sildenafil citrate[69]. For spasticity, there are GABAergic drugs such as baclofen and diazepam and carbamazepine for tremors and ataxia[68-70].

Acute exacerbations

The frequency and the degree of neurological decline generated in the patient are studied when referring to exacerbations. Moreover, they constitute an initial marker of RRMS[4]. At this stage, the recommended initial therapy corresponds to glucocorticoids in high doses and for a short time. Intravenous methylprednisolone (1000 mg/day for 3 to 5 days) or oral prednisone (1250 mg/day) is regularly administered[5,71].

Its action mechanism involves down-regulating proinflammatory cytokine expression levels, preventing immune cells from migrating to the CNS, and inhibiting T cell activation[72]. Therefore, care should be appreciated if the person has an active infection from corticosteroid immunosuppression. Other side effects are mood swings, depression, insomnia, anxiety, hypertension, gastrointestinal upset, osteoporosis, and osteopenia[71,73].

Progression modifiers

There are treatments focused on modifying the pathology progression, reducing the possibility and risk of attack relapses through modulation of the immune function[8]. The first to be approved by the United States Food and Drug Administration (FDA) were beta interferons (β-1a and β-1b) and glatiramer acetate[74]. The mechanism of action of interferons within MS is complex. Nonetheless, it is known that they increase the expression of anti-inflammatory cytokines such as IL IL-5, IL-10, IL-13, and IL-17 and decrease proinflammatory ones such as IL-17, IFN-γ, and TNF-α[75,76]. Additionally, they reduce T cell activation and prevent their adhesion and penetration into the CNS by closing the blood-brain barrier. As for B cells and other APCs, the presentation process is disrupted[76]. Conversely, glatiramer acetate is a synthetic drug structurally resembling myelin basic protein[77]. It is given in a dose of 20 mg/day, and its mechanism of action still needs to be fully understood. It is believed to block the immune system's attack on myelin, creating a protective effect[6,78,79].

Regarding second-line treatments, fingolimod modulates the sphingosine-1 phosphate receptors (S1PR). The receptors are in immune cells such as neutrophils, macrophages, B cells, and Natural Killer (NK) lymphocytes. They are structures of seven transmembrane domains coupled to G proteins, and their effect has been verified in innate and adaptive immunity. Among its outcomes are the modulation of the immune cells' output in the lymph nodes and the recruitment of NK cells and CD8+ T lymphocytes[80-82].

This pharmaceutical product is indicated for MS recurrent forms. Its mechanism of action encompasses the alteration of the T lymphocytes' egress from the lymph nodes, retaining central memory T cells and naïve T cells. Thus, the circulation of CNS autoreactive lymphocytes is reduced[83,84]. It is administered orally, and its most relevant adverse effects include bradycardia, macular edema, infections, and teratogenicity[83].

Based on the evidence with fingolimod, more selective second-generation modulators (siponimod and ozanimod) were settled to improve the safety profile. They are preferred in patients with uninterrupted progression, secondary relapse, or SPMS[4,8,81]. A second-generation drug implies modifications that improve its pharmacological profile concerning the first-generation[85]. It differs from second-line treatment, used when the first choice fails (poor response) or has intolerable adverse effects[86].

Another option is teriflunomide. It is an orally administered product involving pyrimidine synthesis inhibition to block the proliferation and function of active T and B lymphocytes[4,8]. It is indicated for recurrent MS, and its adverse effects include alopecia, hepatotoxicity, and birth defects. Due to the latter, it is recommended to receive contraceptives during treatment and for up to two years afterward[4].

Concerning fumarates (dimethyl fumarate, diroximel fumarate, and monomethyl fumarate) are indicated and approved by the FDA for RRMS, SPMS, and CIS. Their precise mechanism of action is unknown[4]. They are believed to activate the Nrf2/HO-1 signaling pathway. The nuclear factor erythroid 2 - related factor 2 (Nrf2) regulates antioxidant defense systems

in the presence of ROS. It secretes the antioxidant enzyme heme oxygenase-1 (HO-1), generating a neuroprotective effect by diminishing oxidative stress and neuroinflammation[87,88]. Besides, it activates the essential gene transcription for macrophages' phagocytic function, being a key regulator for innate immunity[89].

Another medication is cladribine, an oral prodrug whose mechanism alters DNA synthesis and the consequent B and T lymphocyte depletion. This chlorinated deoxyadenosine analog prevents the production of proinflammatory cytokines by accumulating its triphosphorylated form (Cd-ATP) on lymphocytes, triggering cell death[4,90]. Its interference in DNA synthesis occurs because of structural competition with the natural nucleosides available91. Its side effects are a high risk of malignancies and teratogenicity[4].

Finally, an approach toward highly effective therapies, such as monoclonal antibodies, is currently being sought. The idea is to apply them as a first option, not as a progressive disease treatment. Such a scenario has been suggested by observational studies, which concluded the importance of applying highly effective substances with better long-term results[8].

MONOCLONAL ANTIBODIES AS A THERAPEUTIC OPTION

The breakthrough of monoclonal antibodies meant a scientific advance as a new option for diagnosing and treating cancer, infectious pathologies, and autoimmune disorders. They are based on the immune system's basic functioning and ability to recognize any substance or toxin foreign to the body and generate a response capable of eliminating it[7,92]. B lymphocytes produce glycoproteins called antibodies, which bind to specific antigens so that the cells of the said system recognize them as foreign and eradicate them[93].

These proteins have two light and two heavy chains (**Figure 2**). The four structures are linked to each other by disulfide bonds. Light chains contain one variable and one constant region, while heavy ones are constituted by one variable and three to four constants, depending on the isotype. The variable regions of the four chains make up the antigen-binding fragment (Fab), which comprises the areas of most significant antigens specificity, the hypervariable regions (CDR)[7,94,95]. The constant regions of the heavy chains form the crystallizable fragment (Fc). It binds to diverse receptors, generating an immune response[7,94]. The Fc region provides the antibody with numerous functions: antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and complement-dependent cytotoxicity (CDC)[96,97].

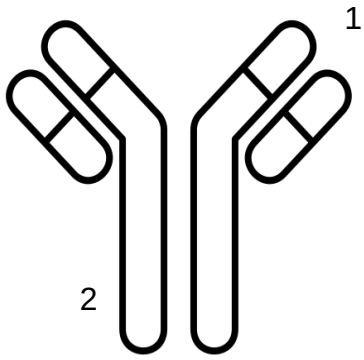

Figure 2. The general structure of an antibody. It shows the Fab [**1**] and Fc [**2**] fragments. The Fab is the variable region and contains the CDRs, which give the antibody specificity for the different antigens. The Fc is a constant region and provides the antibody with effector functions.

Depending on the heavy chain type, they are classified into isotypes. Five are known, which are alpha (IgA), mu (IgM), gamma (IgG), delta (IgD), and epsilon (IgE). IgG is the most abundant in the body and is typically chosen for producing monoclonal antibodies[98,99]. Among the reasons for its choice are the therapeutic advantages offered: high specificity, long half-life (up to 21 days), dosing frequency, an affinity for therapeutic targets that synthetic origin drugs do not possess, and

constant fractions that can be modified to improve characteristics such as pharmacokinetics, affinity, and safety. Another aspect is its weight, which does not exceed 150 kDa, making it permeable to extravascular spaces[99-101].
IgG isotypes are subdivided into IgG1, IgG2, IgG3, and IgG4. Their selection must be made according to the antigen and the mechanism of action required. The IgG isotype subclasses have structural differences in the Fc region, which is why some have more affinity to specific receptors than others. For example, IgG1 and IgG3 have an affinity to activate specific effector pathways, being more efficient against pathogens. Therefore, IgG1 is the most utilized since IgG3 has a short half-life compared to the other subtypes. IgG2 and IgG4 are considered when cell activity attenuation is desired[102].

Monoclonal antibodies classification

Murine

The hybridoma technique produces them. It consists of the B lymphocyte immortalization through fusion with myelomas. These cells mature in a lymphatic organ, typically the spleen, to generate a response against the antigen. The suffix can identify them -omab in the name[7,98,101]. Its prolonged employment demonstrated adverse effects on generating antibodies against the therapeutic antibody (ADAs) and a rapid efficacy loss. Scientific advances have allowed its humanization to reduce them[10].

Chimeric

They are antibodies that maintain the variable region of murine origin, and through genetic engineering techniques, human gene sequences are taken for the constant portions. They are 65% human and 35% murine. With them, an increase in half-life and fewer immunogenic reactions were observed, although the latter is still considerable. The suffix to recognize them is -ximab[7,93].

Humanized

They are 95% of human origin, keeping only the CDRs of the murine source. The genetic techniques to make them are complex and contain limitations. Its suffix is -zumab[7,93].

Fully human

They are produced with transgenic animals that produce human immunoglobulins, making them less immunogenic and better tolerated than other types. They can be differentiated by the suffix -umab[7]. Phage libraries are another available technique. Its implementation enables the development and modification of an extensive gene repertoire, which other procedures do not allow[102].

MONOCLONAL ANTIBODIES AGAINST MULTIPLE SCLEROSIS

Monoclonal antibodies against MS help mainly during the early inflammatory phases. They specifically neutralize the immunological components that attack the CNS. Due to their therapeutic target specificity and high efficacy, they have predictable side effect profiles, few drug interactions, and a potential benefit against MS progressive forms[9,103]. Nonetheless, they exhibit immunosuppressive effects and reactions to the drugs that must be contemplated.

Commercialized antibodies

Natalizumab was the first to be approved by the FDA. Since its introduction and reintroduction in 2004 and 2006, these proteins have gained relevance as a therapeutic option against MS, promoting their research and elaboration[104]. Currently, several disease-modifying therapies are approved by this regulatory authority (ofatumumab, ocrelizumab, natalizumab, and alemtuzumab)[103]. Plus, they are approved by the European Medicines Agency (EMA).
Ofatumumab
It is a recombinant human IgG1k monoclonal antibody directed to the differentiation 20 (CD20) cluster, a transmembrane phosphoprotein highly expressed on the surface of B lymphocytes. It was approved in 2020 by the FDA and in 2021 by the EMA for CIS, RRMS, and SPMS[105,106]. The antibody Fab region is designed to selectively bind to the small and the large

extracellular loops of CD20, which plays a role in B cell development and differentiation and the independent T response activation. This binding provokes T lymphocyte apoptosis via ADCC and CDC[105-107].

Its approval in patients with RRMS was based on the results of two identical, multicentre, double-anonymized, randomized, active-comparator-controlled phase III trials. There were 927 and 955 patients between the ages of 18 and 55 diagnosed with RRMS and SPMS. Subjects received ofatumumab 20 mg once a month or teriflunomide 14 mg daily for up to 30 months[106,107]. The trial demonstrated that the monoclonal antibody was more effective, reducing the annualized relapse rate and progression in people with MS remitting forms[106].

As a complement, three studies on phase II associated this biological therapy with significant reductions in new brain lesions. The findings were observed through MRI[106]. Due to the low serum immunoglobulin levels that can occur with anti-CD20 therapies, those treated may be at risk of serious infections, even though the incidence is low108. Its most frequent unwanted effects are nasopharyngitis, upper respiratory tract infections, headaches, urinary tract infections, and injection-related and injection-site reactions[106,109].

Ocrelizumab

It is a recombinant humanized IgG1 molecule against CD20, approved by both the FDA and the EMA in 2017105, 110, 111. It has a mechanism of action similar to that of ofatumumab, directed against mature and immature B lymphocytes. However, it is indicated for adults with RRMS and PPMS[110-112]. Its approval represented a vital step for PPMS patients, being the first drug approved capable of generating effective long-term lymphocyte depletion[110]. In addition, it offers a treatment regimen once every six months, so it does not require routine monitoring[111].

For the RRMS indication, two identical phase III, double-anonymized, placebo-controlled, manufacturer-sponsored trials were conducted to verify the molecule efficacy against INF β-1a. Both lasted 96 weeks and included 821 and 835 patients between 18 and 55 years. Participants received ocrelizumab 600 mg intravenously every 24 weeks (first dose split administered as 300 mg infusions given two weeks apart followed by subsequent infusions of 600 mg at 24-week intervals) or INF β-1a 44 µg subcutaneously three times per week. The results showed a significant diminution in the annualized relapse rate in patients treated with monoclonal antibodies[110-112].

In the case of the indication against PPMS, a phase III randomized, placebo-controlled investigation was carried out for 120 weeks with a total of 732 patients. People were randomized to receive 600 mg of ocrelizumab, given as two 300 mg intravenous infusions administered two weeks apart every 24 weeks, or placebo. The chosen population was diagnosed with PPMS with ages between 18 and 55 years. Those who received the biological drug showed less progression than the placebo, with no significant difference[110-112].

This product is administered by intravenous infusion. The most frequent adverse effects are moderate infusion reactions, commonly within the first 24 hours, because of type 2 hypersensitivity reactions and cytokine release. Besides, infections due to induced immunosuppression have been reported[105,112], so the drug should be avoided in severely immunosuppressed or cancer patients[113]. Moreover, it is necessary to perform a test for hepatitis B and C before the first dose, as it has been associated with reestablishing its viral replication (suboptimal humoral immune response)[114,115].

Alemtuzumab

Alemtuzumab, formerly Campath-1H, is a recombinant humanized IgG1k targeting the cell surface glycoprotein CD52. It was approved by the EMA in 2013 and the FDA in 2014 for treating RRMS in adults[116-118]. It is considered for patients with an inadequate response to two or more drugs[116] for its safety profile. This active ingredient is designed to bind to the CD52 membrane glycoprotein. Its function remains partially unknown, but its negative charge is presumed to repel and hinder cell adhesion, keeping lymphocytes available for activation[117]. In MS, alemtuzumab binds to T and B cells, reducing the circulating population by ADCC and CDC. In addition, it promotes the repopulation of both lines[119].

A randomized, blinded, active-controlled phase II clinical trial (334 patients) of alemtuzumab (12 or 24 mg/day on five consecutive days, followed by a second therapy course at the exact dosage on three consecutive days at months 12 and 24) versus subcutaneous INF β-1a (44 µg three times a week) was conducted[117,119]. There was a 67% decrease in the relapse rate[117]. Regarding phase III studies, they encompassed 581 and 840 patients. They were designed as randomized, active comparator-controlled, and lasted two years. Both recruited patients with RRMS. The monoclonal antibody was shown to be significantly more effective[117,119]. The EMA approved this drug as the first line since the benefits outweighed the risks[120].

The most common adverse effects include infusion-related reactions such as rash, headache, and fever. More severe events can also occur, such as autoimmune reactions, lung bleeding, cerebrovascular accidents, cephalic cervical artery dissection, kidney damage, and idiopathic thrombocytopenic purpura[118,120]. Furthermore, it is contraindicated in patients with HIV[116]. Another population is those with heart problems. This substance can interfere with the production of cytokines associated with vasospasm in the coronary arteries, promoting cardiovascular event risk[121].

Natalizumab

Natalizumab is an immunomodulatory drug for individuals with RRMS. It is mainly used with people without significant outcomes with at least one traditional medication or who have shown rapid degeneration[122]. It was the first α4 integrin antagonist approved against MS by the FDA in 2004. Nonetheless, it was withdrawn from the market two years later because two cases of progressive multifocal leukoencephalopathy (PML) were diagnosed. Leukoencephalopathy is a rare brain infection seen in severely immunocompromised patients, triggered by John Cunningham virus reactivation[122,123]. This humanized IgG4 monoclonal antibody was designed to identify and bind to the α4β1 integrin of leukocytes involved in inflammatory processes. Binding prevents their migration from blood vessels into the CNS, reduces the immune cells' entry into the inflammatory zone, and reduces nerve damage[123,124].

The most common side effects are urinary tract infections, nasopharyngitis, headaches, dizziness, nausea, joint pain, and tiredness. It must be administered with special care since it favors the development of PML. This risk rises significantly after two or more years of receiving it. Therefore, if there are suspicions of brain infections, the administration should be stopped immediately[124].

The phase III clinical studies included 942 and 1171 participants who presented RRMS. Natalizumab 300 mg intravenously was administered for four weeks against a placebo, although in the second, 30 µg weekly INFβ-1a was administered intramuscularly to all participants. The main discovery is that it reduced the average number of T2 hyperintense lesions for two years and declined the annualized relapse rate, even in conjunction with interferon[124].

Daclizumab

Daclizumab is a humanized IG1 molecule that blocks CD25 and prevents IL-2 binding. This receptor comprises a high-affinity unit and a low-affinity unit. Daclizumab binds to the high-affinity unit, creating a signal that decreases T cell activation and inflammation while activating NK cells due to the binding of soluble IL-2 to the non-high affinity IL-2 receptor[125-128].

For phase II, 24 treatment weeks and 48 follow-up weeks were investigated with 230 patients with either RRMS or SPMS. It was compared against a placebo. This trial investigated the combination therapy of IFN-β and subcutaneous daclizumab at 2 mg/kg every two weeks and 1 mg/kg every four weeks. There was a descent of more than 70% in T2 lesions at high doses[126,128]. In another phase II study, 621 volunteers participated. Treatments provided were subcutaneous daclizumab high-yield process (DAC HYP) in two doses (150 or 300 mg every four weeks) or placebo. This formulation has a distinct glycosylation pattern, changing the DAC binding to Fc receptors and reducing the consequential ADCC activity[129,130]. The therapy administered was randomized for 52 weeks, and quality of life improvement was demonstrated with the biological therapy[128,129].

A double-anonymized, multicenter, controlled, and randomized phase III trial was established, recruiting 1841 patients with RRMS, who were given DAC HYP 150 mg every four weeks (with weekly intramuscular placebo) or intramuscular INF β-1a 30 µg every week (with subcutaneous placebo given every four weeks) for 96 to 144 weeks. The most crucial result brought a 45% relative risk reduction against the monoclonal antibody placebo[128]. This drug was approved by the FDA and EMA in 2016 for RRMS treatment. Nevertheless, secondary autoimmune disease directed primarily against the CNS, liver, and skin resulted in serious adverse events, leading to its withdrawal in 2018[125].

Rituximab

Rituximab is not approved for MS treatment but is employed off-label on certain occasions. It is a glycoprotein of chimeric origin created against the CD20 antigen[9]. In a randomized, double-anonymized, placebo-controlled phase II study directed

at 32 centers in the United States and Canada, a rapid and greater than 95% depletion of peripheral B lymphocytes was demonstrated. Therefore, it could reduce activity in people with RRMS[131].

In another single-center, randomized, double-anonymized, placebo-controlled phase II investigation, it was discovered that in individuals with SPMS, intravenous and intrathecal injection promoted a long-lasting depletion of B cells in the peripheral circulation of 98.79%. In the CSF, a decrease of 79.71% was described. The depletion percentage at the central level was lower than expected, and there was no reduction in the neurofilament light chain (NF-L) biomarker, which indicates axonal damage. Therefore, the immune response inhibition in the CNS could not translate into clinical efficacy[132].

MONOCLONAL ANTIBODIES AGAINST MULTIPLE SCLEROSIS UNDER INVESTIGATION

Some drugs are currently under investigation. They are directed at the B cells' modulation and other therapeutic targets. Next, its main characteristics are described.

Ublituximab

Ublituximab is an Ig1 chimeric antibody that acts on CD20. In a phase II, placebo-controlled, multicenter trial that evaluated its safety and efficacy in patients with RMS, greater than 99% peripheral B-cell depletion was evidenced in the fourth week. Likewise, at week 24, no new or persisting T1-weighted gadolinium-enhancing lesions were seen on any volunteer's brain MRI. Although it acts only on B cells, with its administration, there was a significant reduction in T helper 1 (Th1) lymphocytes, which are pro-inflammatory. Additionally, its safety was determined since only one grade 3 side effect occurred, specifically fatigue[133].

Because of its high efficacy, two phase III, multicenter, double-anonymized, double-dummy, randomized, active-controlled studies were performed in parallel in individuals with RRMS. Subjects received intravenous ublituximab (150 mg on day 1, followed by 450 mg on day 15 and at weeks 24, 48, and 72) plus oral placebo or oral teriflunomide (14 mg once daily starting on day one and continuing until the last day of week 95). The biological medication demonstrated statistically significantly superior efficacy to the chemical synthesis one, reflected in lower annualized relapse rates and fewer brain lesions on MRI. The most frequent side effects were infusion-related reactions, headache, nasopharyngitis, fever, and nausea[134].

Inebilizumab

Inebilizumab is an afucosylated IgG1k humanized molecule directed against the CD19 antigen of B cells. The afucosylation gives it better characteristics to bind to its target and increases ADCC in effector cells. This coreceptor is expressed from the early B lymphocyte development until their differentiation into plasma cells. In a multicentre, randomized, blinded, placebo-controlled, dose escalation, phase 1 study in patients with RRMS, the following treatments were administered: inebilizumab 30, 100, or 600 mg intravenous on days 1 and 15, or inebilizumab 60 or 300 mg subcutaneous on day 1. The monoclonal antibody proved to be safe and tolerable. It also showed at least 90% B cell depletion compared to the placebo, including through the 24-week follow-up period[135]. To date, this is the only completed investigation.

GNbAC1

GNbAC1 is a humanized IgG4-type antibody against the multiple sclerosis-associated retrovirus (MSRV)-Env, expressed by retroviral genetic information embedded in human genome fragments. Its expression has been associated with cancer, neurodegeneration, and autoimmunity pathophysiology. In MS, there is a more significant presence of brain lesions. Therefore, the protein is believed to activate the immune response, promoting acute and chronic inflammation in the CNS and impeding the differentiation of oligodendroglial precursor cells, impairing remyelination[136].

In a phase IIa randomized clinical study, with a one-year follow-up, the drug proved well tolerated when administered in doses of 2 or 6 mg/kg in patients with RRMS and PPMS since no hypersensitivity or immunogenicity reactions were recorded. As a complement, there was no sign of a pathological activity increase, and it was inferred that it does not have immunosuppressive activity[137].

Elezanumab

Elezanumab is a human protein that goes against the repulsive guidance molecule a (RGMa)[9]. It is found in axonal tissues and neurons of the CNS and participates in embryonic morphogenetics. Also, it has cell adhesion properties by interacting with neogenin, promoting the formation of cell aggregates, and it is expressed by dendritic cells in the bone marrow, participating in the inflammatory cells' invasion to the CNS during autoimmune encephalomyelitis through binding to CD4+ T lymphocytes neogenin and their adhesion improvement[138].

In MS, it is upregulated and is involved in axonal growth and myelination inhibition. Thus, difficulties occur in tissue regeneration after inflammatory injury. In phase 1, a double-anonymized, placebo-controlled, randomized, escalating multiple-dose 29-week study, patients with RRMS or SPMS received 150, 600, or 1800 mg of the monoclonal antibody. There were no improvements or pathology deterioration concerning the placebo. Safety and tolerance were detected, with headaches being the most frequent side effect[139].

CONCLUSION

Multiple sclerosis is incurable, and its prevalence has increased over the years. It affects the myelination of neurons, presenting symptoms that compromise the patient's quality of life. Traditional therapies are insufficient to control symptoms and reduce neurological deterioration. In addition, they carry numerous adverse effects. Currently, monoclonal antibodies are being studied. Some have been commercialized and later withdrawn, such as natalizumab and daclizumab. Still, there are approved and successful therapies in effectiveness and tolerance, such as ofatumumab, ocrelizumab, alemtuzumab, and rituximab (off-label). Other therapeutic targets such as ublituximab, inebilizumab, GNbAC1, and elezanumab continue to be investigated. Therefore, research must continue to spread the available therapeutic options for the population with this illness.

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DATA AVAILABILITY

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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